No. 22-56014

IN THE UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

UNITED STATES OF AMERICA,

Plaintiff-Appellant,

v.

CALIFORNIA STEM CELL TREATMENT CENTER, INC., a California corporation; CELL SURGICAL NETWORK CORPORATION, a California corporation; ELLIOT B. LANDER, M.D., individual; MARK BERMAN, M.D., individual,

Defendants-Appellees.

On Appeal from the United States District Court
for the Central District of California

BRIEF FOR APPELLANT

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TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Cases: **Page(s)**

Statutes:

Regulations:

Rule:

Other Authorities:

STATEMENT OF JURISDICTION

The United States brought this action against defendants under the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.* The district court had jurisdiction under 21 U.S.C. § 332(a) and 28 U.S.C. §§ 1331, 1345. The district court entered final judgment on August 30, 2022. 1-ER-2 (order); *see* 1-ER-3-21 (findings of fact and conclusions of law). The government filed a timely notice of appeal on October 27, 2022. 11-ER-1646; *see* Fed. R. App. P. 4(a)(1)(B). This Court has jurisdiction under 28 U.S.C. § 1291.

STATEMENT OF THE ISSUES

Defendants harvest adipose tissue—essentially, fat—from patients. Defendants then extensively alter that tissue through chemical and mechanical steps to create what they call stromal vascular fraction (SVF). This substance comprises various kinds of cells that were previously dispersed and embedded throughout the adipose tissue as well as cellular debris created by the processing steps. In some instances, defendants also take further steps to replicate the cells and then bank the resulting substance for future use. Defendants market SVF products as treatments for an array of medical conditions including Alzheimer's disease, cancer, arthritis, and macular degeneration. This appeal presents the following questions:

1. Whether the SVF products are "drugs" under the FDCA, which defines the term "drug" to include articles that are "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease," or that are "intended

to affect the structure or any function of the body," and any components of such articles. 21 U.S.C. § 321(g)(1)(B)-(D).

2. If so, whether defendants' manufacture and subsequent administration of their SVF product during a single surgical procedure is entirely excepted from regulation by the Food and Drug Administration (FDA) under what is commonly called the "same surgical procedure exception," which canonically excepts skin grafts and vascular grafts used in artery bypass surgery and only applies to "an establishment that removes [human cells, tissues, or cellular or tissue-based products] from an individual and implants such [articles] into the same individual during the same surgical procedure." 21 C.F.R. § 1271.15(b).

PERTINENT STATUTES AND REGULATIONS

Pertinent statutes and regulations are reproduced in the addendum to this brief.

STATEMENT OF THE CASE

I. Statutory and Regulatory Background

A. The Federal Food, Drug, and Cosmetic Act

Congress enacted the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.*, to protect the public health by ensuring that drugs and other specified products are safe, effective, and properly labeled. *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133-134 (2000); *United States v. Dotterweich*, 320 U.S. 277, 280-281 (1943); *see also* 21 U.S.C. § 393(b)(2) (describing the mission of FDA). Among other

things, the FDCA applies to all "drug[s]," which include articles that are "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease," or that are "intended to affect the structure or any function of the body," and any components of such articles. 21 U.S.C. § 321(g)(1)(B)-(D); *see also* 21 C.F.R. § 201.128 (defining intended use). The Supreme Court has long explained that "the word 'drug'" in the FDCA "is a term of art for the purposes of the Act" and is broader than "the strict medical definition of that word." *United States v. An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 793 (1969). The Court has added that "Congress fully intended that the Act's coverage be as broad as its literal language indicates." *Id.* at 798.

The FDCA establishes various requirements for drugs, which are implemented by FDA regulations, and the Act prohibits a number of specified acts involving drugs and other regulated articles. *See, e.g.*, 21 U.S.C. §§ 331, 351, 352. Although this appeal does not call upon the Court to address the scope of these requirements, some brief legal background may aid the Court's review. In short, and as directly relevant here, the FDCA prohibits any person from taking any act with respect to a drug "while such article is held for sale . . . after shipment in interstate commerce" that results in the drug "being adulterated or misbranded." *Id.* § 331(k). Among other things, a drug is adulterated if it is manufactured without proper safety controls and misbranded if it lacks adequate directions for use. *See, e.g.*, *id.* § 351(a)(2)(B) (adulteration); *id.* § 352(f)(1) (misbranding). A drug generally lacks adequate directions for use unless FDA has authorized the drug's labeling, such as when FDA approves a new drug or permits

clinical study of the drug. *See, e.g.*, *United States v. Regenerative Scis., LLC*, 741 F.3d 1314, 1323-1324 (D.C. Cir. 2014); *see also* 21 U.S.C. § 355(b), (i); 21 C.F.R. §§ 201.100(c)(2), 201.115. A drug is "held for sale" not only when it is held by wholesalers and retailers, but also when it is held by healthcare professionals for use in their practice. *See United States v. Kaplan*, 836 F.3d 1199, 1208-1211 (9th Cir. 2016).

B. Human Cells, Tissues, or Cellular or Tissue-Based Products

1. This case involves the application of the FDCA to human cells, tissues, or cellular or tissue-based products that are intended for use in the treatment of diseases. These products are known as "HCT/P's," a term defined by FDA regulation to refer to "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient," including bone, ligament, skin, heart valves, reproductive tissue, and various cells. 21 C.F.R. § 1271.3(d). FDA regulates, among other things, "biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies." FDA, *About CBER*, https://perma.cc/Y4CT-2Y7U; *see* 4-ER-486-487. These include both "products that are made with [a] patient's own cells or tissues" and "products that are made with donors['] typically or someone else's cells or tissues." 4-ER-487.

HCT/P's are potentially subject to regulation both under the FDCA and under the Public Health Service Act (PHSA), 42 U.S.C. § 201 *et seq.* HCT/P's come within the FDCA's definition of "drug" if they are intended to diagnose, cure, treat, mitigate, or prevent diseases or are intended to affect human bodily function or structure. *See* 21

U.S.C. § 321(g)(1). HCT/P's are also subject to regulation as "biological product[s]" under the PHSA. *See* 42 U.S.C. § 262(i)(1) (defining the term "biological product" to mean a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product[] . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings"). An article can be both a drug and a biological product. *See Regenerative Scis.*, 741 F.3d at 1321.

2. FDA has long recognized that different HCT/P's may pose different levels of risk to health and safety. FDA accordingly developed a "tiered, risk-based approach to regulating HCT/P's," under which "the regulation of different types of human cells, tissues, and cellular and tissue-based products will be commensurate with the public health risks presented." 66 Fed. Reg. 5447, 5447, 5449 (Jan. 19, 2001). The framework is particularly aimed at "preventing unwitting use of contaminated tissues," "preventing improper handling or processing that might contaminate or damage tissues," and "ensuring that clinical safety and effectiveness is demonstrated for tissues that are highly processed" or meet other criteria that raise questions of safety and effectiveness. FDA, *Proposed Approach to Regulation of Cellular and Tissue-Based Products* 6 (Feb. 28, 1997), https://perma.cc/M2QS-PPNC (1997 Proposed Approach).

In some cases, the risks associated with HCT/P's are adequately addressed under Section 361 of the PHSA, which provides FDA with regulatory authority to "prevent the introduction, transmission, or spread of communicable diseases." 42 U.S.C.

§ 264(a).[1] When an HCT/P meets certain regulatory criteria, it will be regulated exclusively pursuant to Section 361 and will not be regulated under the FDCA or under other provisions of the PHSA. *See* 21 C.F.R. § 1271.10. To qualify for this limited form of regulatory oversight, HCT/P's must meet specified criteria, including that they be "minimally manipulated" and be "intended for homologous use only"—that is, be intended to "perform[] the same basic function or functions in the recipient as in the donor." *Id.* § 1271.10(a)(1)-(2); *see id.* § 1271.3(c). For example, a cornea that is transplanted from a donor to a recipient to replace the recipient's damaged cornea would likely satisfy the "minimally manipulated" and "homologous use" requirements and so could be regulated solely under Section 361 of the PHSA and FDA's implementing regulations under 21 C.F.R. Part 1271.

FDA regulations also identify certain circumstances where an establishment that uses HCT/P's is excepted from FDA's HCT/P regulation altogether. For example, establishments that use HCT/P's "solely for nonclinical scientific or educational purposes" are not subject to FDA regulation under Part 1271. 21 C.F.R. § 1271.15(a). FDA has similarly excepted commercial couriers, *id.* § 1271.15(c), facilities that "only receive[] or store[] HCT/P's solely for implantation, transplantation, infusion, or transfer within [the] facility," *id.* § 1271.15(d), and establishments that "only recover[]

[1] The statute originally granted this authority to the Surgeon General, but those functions were later transferred to the Department of Health and Human Services (HHS). *See* 42 U.S.C. § 202. HHS has delegated this authority to FDA. *See FDA Staff Manual Guides*, vol. II, SMG 1410.10 (Feb. 22, 2023), https://perma.cc/263L-69NU.

reproductive cells or tissue and immediately transfer[] them into a sexually intimate partner of the cell or tissue donor," *id.* § 1271.15(e).

Directly relevant here, FDA has excepted from regulation any "establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure." 21 C.F.R. § 1271.15(b). This is commonly known as the same surgical procedure exception. *See* 1-ER-14-15; *United States v. U.S. Stem Cell Clinic*, 998 F.3d 1302, 1305 (11th Cir. 2021); FDA, *Same Surgical Procedure Exception Under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception* (Nov. 2017), https://perma.cc/MC76-C2SB (FDA Guidance). As FDA explained when proposing this exception, "communicable disease risks, as well as safety and effectiveness risks, would generally be no different [for cases falling into this exception] from those typically associated with surgery." 1997 Proposed Approach 12.

FDA has provided guidance to regulated entities concerning the same surgical procedure exception. Consistent with its longstanding approach to the exception, FDA's guidance states that "cells or tissues that are removed from an individual and implanted into the same individual without intervening processing steps beyond rinsing, cleansing, sizing, or shaping, raise no additional risks of contamination and communicable disease transmission beyond that typically associated with surgery." FDA Guidance 3. Common examples include "autologous skin grafting" and "coronary artery bypass surgery involving autologous vein or artery grafting." *Id.* at 5. FDA guidance explains that any establishment that performs processing steps other

than rinsing, cleansing, sizing, or shaping on an HCT/P prior to implantation typically would not qualify for the same surgical procedure exception, because such processing of the HCT/P "raises safety concerns, such as contamination and cross-contamination, beyond those typically associated with surgery." *Id.* at 7.

II. The Present Controversy

A. Factual Background

Defendants in this case are two doctors and their businesses. 1-ER-4-5.[2] Defendants offer two types of treatments that are relevant here.[3] First, defendants perform what they call the "SVF Surgical Procedure" where during one outpatient procedure, they remove adipose tissue—essentially, fat—from patients, and use mechanical and chemical processes to create a mixture of cells and cell debris called stromal vascular fraction (SVF), which is then administered to the patient. 1-ER-5-8. Second, defendants perform the same steps in what they call the "Expanded MSC

[2] On May 18, 2023, defendants filed a Suggestion of Death, notifying the Court that one of the individual defendants, Dr. Mark Berman, died on April 19, 2022. That filing did not suggest that the remaining defendants—an individual and several businesses—no longer wish to engage in the conduct at issue. The government therefore proceeds on the understanding that there remains a live controversy as to these remaining defendants.

[3] The case originally involved an additional treatment, but defendants report that they have ceased providing it, and defendants also lack access to a necessary component. The district court accordingly dismissed that aspect of the case for lack of standing. *See* 1-ER-19-20. The government is not appealing that holding.

Procedure" but with the cellular isolation occurring at an outside tissue bank and the cells then being replicated and stored for later use. 1-ER-8-11.

Defendants begin by removing adipose tissue using liposuction. 1-ER-7; *see, e.g.*, 6-ER-701. The adipose tissue primarily comprises fat cells but also includes an array of other types of cells, mostly "embedded in an extracellular matrix." 6-ER-694; 6-ER-703-704; 6-ER-711-712. The "extracellular matrix" does not just hold fat cells in place but also is biologically "active and contains growth factors that cells would respond to." 6-ER-708.

Defendants then use various chemical and mechanical steps to create SVF—essentially a collection of certain types of cells that were previously dispersed and embedded throughout adipose tissue, as well as cellular debris. 1-ER-7-9; *see* 10-ER-1604-1643. For what defendants call the "SVF Surgical Procedure," these steps typically occur while the patient is out of the room and sits in street clothes in a waiting room. *See* 1-ER-7; 3-ER-214-215. For what defendants call the "Expanded MSC Surgical Procedure," the processing occurs at an outside tissue bank. *See* 1-ER-8-9; 3-ER-175-176.

Defendants first use an "enzyme blend," 6-ER-701, which is "incubated" with the adipose tissue "at an elevated temperature to optimize the enzyme's activity." 6-ER-712-713. The enzymes "break certain bonds in proteins" and "obliterat[e] the main structural components" of adipose tissue, effectively "[d]igest[ing]" the tissue. 6-ER-714-716. One expert witness offered an analogy to explain the difference

between ordinary cutting and this sort of enzymatic digestion: "If you have a very soft wood dowel," she explained, "you can take an X-ACTO knife and cut it into two pieces." 6-ER-720. "But using enzymes would be like unleashing a bag of termites, a brood of termites onto the dowel." 6-ER-720.

Defendants then use "several processing steps" that involve "centrifugation" and "washing." 6-ER-701. The centrifuge separates and enables removal of certain fat molecules, blood, and local anesthetic. 6-ER-701; 6-ER-712. Then, this "digested" substance is further processed by "pushing" the "slurry" through a filter to create "a small cellular concentrate that is suspended in liquid." 6-ER-701; 6-ER-754-755. As noted, in defendants' "expanded" SVF process, an outside tissue bank further processes the substance to replicate cells. 1-ER-8-9.

The final SVF is a "liquified mixture of cells and cell debris." 7-ER-1054. This includes "[a] heterogenous mixture of cells" that normally are embedded throughout the "extracellular matrix" in adipose tissue. 6-ER-756-757. One defendant testified that it is like "a potpourri" that includes "four different types of stem cells," as well as "a number of other cells." 8-ER-1252-1253.

The final step in what defendants call their SVF surgical procedures involves combining the SVF with saline and administering the mixture to patients based on what condition defendants are purporting to treat. The SVF product might be "injected into the knee" or "dripped with an IV into the bloodstream." 3-ER-175. Among other things, defendants use "intravenous" delivery, "meaning into the systemic circulation";

"intra-articular" delivery, meaning "inside one's joint"; "intrathecal[]" delivery, meaning "around one's spinal cord"; "nebulization, meaning through inhalation"; "intraventricularly, inside one's brain"; and "around the eye." 5-ER-545; *see, e.g.*, 4-ER-331; 10-ER-1416; 10-ER-1425; 10-ER-1503-1504; 10-ER-1591.

Defendants use their SVF products to treat a variety of medical conditions. These include chronic obstructive pulmonary disease (COPD), various heart conditions, joint diseases, multiple sclerosis, Amyotrophic Lateral Sclerosis (ALS) or "Lou Gehrig's Disease," muscular dystrophy, Parkinson's disease, macular degeneration, Crohn's disease, dementia, alopecia, and erectile dysfunction. *See, e.g.*, 2-ER-55; 2-ER-69; 7-ER-1060-1069; 10-ER-1406; 10-ER-1428-1429; 10-ER-1443; 10-ER-1483-1486. Among other things, defendants market SVF to "[p]atients who are looking for non-surgical alternatives to their degenerative disorders." 8-ER-1127-1128; *see* 10-ER-1378. One defendant called SVF "liquid magic." 7-ER-1060; *see* 7-ER-1060-1065.

The creation and use of these kinds of cellular-based products is a "relatively young field" lacking "good quality studies." 5-ER-529-530. Potential risks include stem cells developing into the wrong "type" of tissue "in the wrong place" or "formation of tumors." 5-ER-537. "[A]dipose-derived cellular therapies" have been linked to "systemic inflammatory reactions," "blood clots," and "pulmonary embolism." 5-ER-539-540. The record includes examples of patients suffering serious complications after undergoing defendants' treatments. *See* 10-ER-1499-1500; *see, e.g.*, 8-ER-1099-1102;

10-ER-1515-1519; 10-ER-1561-1562; *see also* 7-ER-860-861 (noting the absence of proper procedures to identify, record, and track adverse events).

B. Procedural History

1. In 2017, after defendants gave a public interview about their treatments, FDA conducted inspections of defendants' facilities. 2-ER-62-63; 2-ER-82; *see* 10-ER-1415-1482; 10-ER-1491-1514. FDA then informed defendants that the SVF products manufactured from adipose tissue are drugs under the FDCA and biological products under the PHSA and are subject to the applicable statutory and regulatory requirements. 8-ER-1111-1113. FDA further informed defendants that FDA has not excepted defendants' activities by regulation. 8-ER-1111-1113. Thus, FDA explained, defendants would need to submit a proper biologics license application and their products could only be used in humans after an investigational new drug application is in effect. 8-ER-1111-1113; *see* 21 U.S.C. § 355(i); 42 U.S.C. § 262(a)(3); *see generally* 21 C.F.R. pt. 312.

Defendants responded by asserting that the FDCA and other FDA regulations do not apply to their activities, and they are not required to obtain any approvals or remedy various health and safety defects that FDA identified. 2-ER-40 (stipulated fact 12); *see* 7-ER-922; *see also* 2-ER-63; 2-ER-82.

The United States filed this civil action in May 2018, alleging that defendants violate the FDCA by improperly manufacturing and labeling the SVF products. 2-ER-78-81. Because the government alleged continuing noncompliance, it sought an

injunction barring defendants from taking any action that led to the continued misuse of the SVF products. 2-ER-81-84.

2. The government moved for summary judgment, which the district court denied. 1-ER-22-34. Although the government's motion concerned all of defendants' SVF treatments, the court solely addressed what it called the "SVF Process" or "SVF Procedure" and whether that was excepted from regulation by the regulatory "same surgical procedure exception." 1-ER-31-34. The government argued that because adipose tissue was removed from the body and the SVF product was later implanted, the procedure did not involve "remov[ing] HCT/P's from an individual and implant[ing] *such* HCT/P's into the same individual." 21 C.F.R. § 1271.15(b) (emphasis added).

The district court disagreed. 1-ER-32-34. The court noted that the regulations governing HCT/P's define HCT/P's as including both "'cells' and 'cellular-based products,'" and the court stated that "cells can only be removed from a patient along with . . . larger systems," such as "tissues and organs." 1-ER-32. If the exception "demanded the removal to be characterized by the largest system that was removed," the court reasoned, "it could never be applied to the removal and implantation of a cell." 1-ER-32. The court therefore concluded that to avoid rendering aspects of the HCT/P definition "superfluous," the same surgical procedure exception "must permit characterizations focused on smaller units." 1-ER-32.

The district court additionally stated that "a characterization that focuses on the target of the removal is more reasonable" because "most if not all surgical removals take out more biological matter than what was targeted"—for example a skin graft or artery bypass "may remove some blood" or "more" tissue "than what will ultimately be needed." 1-ER-33. The court noted FDA guidance citing skin grafts and artery bypass as canonical examples and explaining that a surgeon still implants "such HCT/P" even when there is "'rinsing [and] cleansing' or 'sizing and shaping'" before reimplanting the HCT/P that was removed. 1-ER-33-34 (alteration in original). The court concluded that this same "logic" applies to defendants' SVF treatment because defendants remove various cells within adipose tissue and "use enzymes and a centrifuge to isolate the targeted HCT/P's." 1-ER-33.

The district court declined to give deference to FDA's interpretation of its regulation because the court found the regulation "unambiguous." 1-ER-33-n.14. The court stated, in particular, that FDA's distinction between the rinsing and cutting performed on a skin graft and the chemical digestion and filtration performed to create SVF from adipose tissue is "unreasonable" and "inconsisten[t]." 1-ER-33-n.14.

The court did not conclude that defendants prevailed as a matter of law, however, because it identified a disputed factual issue: whether the cells in SVF "remain unaltered" between when they are removed from adipose tissue and later reintroduced to the body. 1-ER-34. The court therefore left it to trial to determine whether "the SVF Procedure alters the SVF cells." 1-ER-34.

3. Following a bench trial, the district court ruled for defendants in pertinent part and denied any injunctive relief. 1-ER-3-21. The court held that neither the "SVF Surgical Procedure" nor the "Expanded MSC Surgical Procedure" involve the manufacture or receipt of "drugs." 1-ER-12-14; 1-ER-16; 1-ER-18-19. The court did not hold that SVF or the SVF products fail to satisfy any aspect of the FDCA's definition of a "drug," which includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "intended to affect the structure or any function of the body," and any components of such articles. 21 U.S.C. § 321(g)(1)(B)-(D). Instead, the court observed that, like drugs, "surgical procedures . . . are also intended for the diagnosis, cure, mitigation, treatment, or prevention of disease." 1-ER-12-13. The court observed that another provision of the FDCA disclaims any efforts to "limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient." 1-ER-13 (quoting 21 U.S.C. § 396). And the district court noted a statement by the Supreme Court, in another context, that the FDCA disclaims "any intent to directly regulate the practice of medicine." 1-ER-13 (quoting *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 (2001)).

The district court declared that "[t]he line between 'drug' and 'procedure' is especially muddy when licensed medical doctors enter a patient's body, extract that patient's cells, and reintroduce those cells to that patient after some amount of cellular processing." 1-ER-13. From that premise, the court concluded that the SVF products

used in defendants' treatments are not "drugs." 1-ER-13-14. In later reiterating that defendants' "Expanded" SVF treatment (which involves replicating cells and banking the SVF) does not involve the creation of a drug, the court added that SVF comprises "human cells removed from patients and then reintroduced into those same patients," and these cells "are not fungible goods that can be sold, mass produced, or patented." 1-ER-18-19 (citing *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 579 (2013)).

Although the conclusion that neither treatment involved the creation of a "drug" sufficed to enter judgment for defendants, the court further concluded that the "SVF Surgical Procedure" is also excepted from any regulation by the "Same Surgical Procedure Exception." 1-ER-14-18. Resolving the factual issue that it had deferred at the summary-judgment stage, the court found that the "SVF Cells are not altered, chemically or biologically." 1-ER-8; *see* 1-ER-16-17 (stating that the process "does not alter the biological characteristics of the SVF Cells" but qualifying that after processing, the cells' "surface marker expression remains *similar*, and their viability does *not significantly* change" (emphases added)).

The district court otherwise adhered to the analytical approach it had applied at the summary-judgment stage. *See* 1-ER-14-16. The court again pointed to the general definition of HCT/P's and stated that defendants remove "adipose tissue," which "consists of human cells," and the SVF product that defendants then implant "contains such cells." 1-ER-14. The court's analysis of the same surgical procedure exception

applied only to the "SVF Surgical Procedure," however, because the "Expanded MSC Surgical Procedure" does not occur "during a single" procedure, and the court thus concluded that it is not subject to the exception. 1-ER-15.

SUMMARY OF ARGUMENT

I. Defendants' SVF products readily meet the statutory definition of drugs. The FDCA defines the term "drug" as including articles that are "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease," or that are "intended to affect the structure or any function of the body," and any components of such articles. 21 U.S.C. § 321(g)(1)(B)-(D). Defendants market their SVF products as treatments for a variety of diseases or conditions, including arthritis, stroke, ALS, multiple sclerosis, macular degeneration, Parkinson's disease, and diabetes. The products are therefore "intended for use in the . . . cure, mitigation, [and] treatment" of disease and are also "intended to affect the structure or [m]any function[s] of the body," *id.* Two other courts of appeals have correctly indicated that products of this type are therefore "drug[s.]" *United States v. U.S. Stem Cell Clinic, LLC*, 998 F.3d 1302, 1306 (11th Cir. 2021); *United States v. Regenerative Scis., LLC*, 741 F.3d 1314, 1319 (D.C. Cir. 2014). And the Supreme Court has confirmed that the statutory definition of a "drug" is expansive and that "Congress fully intended that the Act's coverage be as broad as its literal language indicates." *United States v. An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 793, 798 (1969).

Defendants' argument, adopted by the district court, seeks an atextual exception to the statutory definition of a drug. Defendants provide no sound reason for adopting such an exception. The district court's suggestion that defendants' creation and use of SVF is a "procedure" misunderstands that the FDCA regulates the SVF substance that is being introduced into the patient, not the procedure by which defendants harvest and then inject or otherwise implant that substance into patients. *See Regenerative Scis.*, 741 F.3d at 1319. Contrary to the district court's reasoning, the fact that FDA does not generally prohibit prescriptions of FDA-approved or cleared drugs or devices for uses not approved or cleared by the agency has no bearing on whether a substance is a drug or whether FDA can regulate drugs that have not been approved for any use. And it is irrelevant that each customized SVF treatment cannot be "mass produced" or that drugs comprising only human cells may not be patentable.

II. Defendants have also not met their burden of establishing that they are entirely excepted from regulation under 21 C.F.R. § 1271.15(b), which provides that an "establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure" is excepted from FDA regulations in Part 1271. The HCT/P that defendants remove from patients—adipose tissue—is indisputably different from the HCT/P that defendants later administer to patients—the SVF product. Therefore, as the Eleventh Circuit held in a similar case, the SVF product is not "such HCT/P[]" within the meaning of FDA's regulation, and the same surgical procedure exception does not apply. *See U.S. Stem Cell*, 998 F.3d

at 1309-1310. That reading of the plain text is consistent with the structure, history, and purpose of FDA's regulations, all of which show that the agency sought to limit this exception to a narrow subset of medical procedures that involve little or no processing of tissue and that pose risks no greater than that of ordinary surgery. Defendants' removal of adipose tissue and subsequent extensive processing of that tissue falls outside that category.

The district court's contrary conclusion rested on its view that the differences between adipose tissue and the SVF product can be disregarded because the regulatory exemption should be applied on the level of individual cells. According to the district court, what matters is that defendants remove cells that exist in various parts of adipose tissue and later end up in the final SVF product. This interpretation of the same surgical procedure exception rests on an implausible reading of the regulatory text. This interpretation also cannot be reconciled with the structure and purpose of this very narrow exception to FDA's regulatory scheme. It would read the same surgical procedure exception as permitting nearly limitless manipulation and recombination of cells and tissues. And it would allow a broad category of HCT/P's, however risky, to be implanted without any regulation whatsoever.

The linchpin of the district court's reasoning was its reliance on the general definition of an HCT/P in 21 C.F.R. § 1271.3(d) that is applicable throughout the provisions governing regulation of HCT/P's. The regulations define HCT/P's to mean "articles containing or consisting of human cells or tissues that are intended for

implantation, transplantation, infusion, or transfer into a human recipient." 21 C.F.R. § 1271.3(d). The court erred by stating that cells cannot be removed separate from surrounding tissue or larger systems and then concluding that FDA's approach of looking to the actual tissue that is removed would render references to cells "superfluous." Cells can be removed in isolation, and these regulations, in any event, address an area of evolving science. More significantly, the definition of HCT/P's is not limited to the same surgical procedure exception but rather applies throughout the entire regulatory structure governing HCT/P's. *See* 21 C.F.R. § 1271.3 (establishing definitions for 21 C.F.R. Part 1271). Thus, the reference to cells would not be superfluous even if it served no function when applied to this particular exception.

FDA's interpretation is the most natural reading of the text and the only one that makes sense in context, and it should be upheld on that ground. *See U.S. Stem Cell*, 998 F.3d at 1310 ("we hold the same surgical procedure exception unambiguously does not apply"). But even if the regulation were not clear, FDA's reading of the regulation would be entitled to deference. FDA's interpretation has been consistent throughout the twenty-year lifespan of this rule; it implicates FDA's scientific, health, and safety expertise; and it reflects the agency's considered views. Under these circumstances, as the Supreme Court recently confirmed, deference is appropriate to FDA's official, considered, and expert view. *See Kisor v. Wilkie*, 139 S. Ct. 2400, 2415-2417 (2019).

STANDARD OF REVIEW

This Court reviews the district court's "conclusions of law and mixed questions of law and fact de novo," and "factual findings are reviewed for clear error." *Bax v. Doctors Med. Ctr. of Modesto, Inc.*, 52 F.4th 858, 865 (9th Cir. 2022).

ARGUMENT

I. Defendants' SVF Products Are Drugs Under The Statutory Definition

A. The FDCA defines the term "drug" as including articles that are "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease," or that are "intended to affect the structure or any function of the body," and any components of such articles. 21 U.S.C. § 321(g)(1)(B)-(D). Defendants' SVF products readily meet that definition. These products are marketed as treatments for a variety of diseases or conditions, including arthritis, stroke, ALS, multiple sclerosis, macular degeneration, Parkinson's disease, and diabetes. *See, e.g.*, 2-ER-55; 2-ER-69; 7-ER-1060-1069; 10-ER-1406; 10-ER-1428-1429; 10-ER-1443; 10-ER-1483-1486. There should be no serious dispute that defendants' products are "intended for use in the . . . cure, mitigation, [and] treatment" of disease and are also "intended to affect the structure or [m]any function[s] of the body," 21 U.S.C. § 321(g)(1)(B)-(D).

In a case involving a different clinic, the Eleventh Circuit indicated that SVF products satisfy the statutory definition of "drug." *United States v. U.S. Stem Cell Clinic, LLC*, 998 F.3d 1302, 1306 (11th Cir. 2021). As that court explained, "[w]hile the lay

person may not think of stem cells as a 'drug,' the FDCA's definition of that word is expansive." *Id.* The D.C. Circuit has likewise explained that products of this type satisfy the plain-language definition of "drug." *United States v. Regenerative Scis., LLC*, 741 F.3d 1314, 1318, 1319 (D.C. Cir. 2014). The district court identified no court that has reached the opposite conclusion.

B. Defendants' argument, adopted by the district court, seeks an atextual exception to the statutory definition of a drug. But "[w]hen a statute includes an explicit definition," courts "must follow that definition." *Tanzin v. Tanvir*, 141 S. Ct. 486, 490 (2020) (quotation marks omitted). The Supreme Court long ago confirmed that "the word 'drug'" in the FDCA "is a term of art for the purposes of the Act" and "encompass[es] far more than the strict medical definition of that word." *United States v. An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 793 (1969). The Court added that "Congress fully intended that the Act's coverage be as broad as its literal language indicates." *Id.* at 798; *accord Baker v. United States*, 932 F.2d 813, 814 (9th Cir. 1991). Indeed, in a statute like the FDCA, which addresses a range of articles in an area with constantly evolving science, "the presumed point of using general words is to produce general coverage—not to leave room for courts to recognize ad hoc exceptions." Antonin Scalia & Bryan A. Garner, *Reading Law: The Interpretation of Legal Texts* 101 (2012); *see Massachusetts v. EPA*, 549 U.S. 497, 532 (2007); *cf.* 21 U.S.C. § 356(g) (2016 amendment directing FDA to establish an expedited approval pathway for certain "cell therap[ies]" and "human cell and tissue products"). This Court has also made clear that

"[t]he FDCA is to be interpreted broadly in order to protect public health." *United States v. Kaplan*, 836 F.3d 1199, 1208 (9th Cir. 2016); *see id.* at 1210.

The district court provided scant explanation for why such an atextual exception was warranted. The court reached its conclusion by deeming defendants' creation and use of SVF products a "procedure" and observing (1-ER-13) that the FDCA "disclaims any intent to directly regulate the practice of medicine," *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 (2001) (citing 21 U.S.C. § 396). But the FDCA regulates the SVF substance that is being introduced into the patient, not the procedure by which defendants inject or otherwise implant that substance into patients. *See Regenerative Scis.*, 741 F.3d at 1319 (explaining that "[n]otwithstanding" defendants' "attempt to characterize this case as an effort by the FDA to 'restrict[] the use of an autologous stem cell *procedure*' the focus of the FDA's regulation is the *Mixture*" (second alteration in original) (citation omitted)). The FDCA establishes various requirements for drugs, and the Act prohibits a number of specified acts involving drugs, even when they involve a doctor purporting to treat a patient. *See* 21 U.S.C. §§ 331, 351, 352; *see also Kaplan*, 836 F.3d at 1208-1211.

FDA's role in determining the availability of therapeutic drugs and biological products inevitably affects physicians who seek to create, use, or prescribe those products; this does not mean that FDA is regulating the practice of medicine. *See, e.g.*, *Regenerative Scis.*, 741 F.3d at 1319; *United States v. 9/1 Kg. Containers*, 854 F.2d 173, 176-177 (7th Cir. 1988); *United States v. Evers*, 643 F.2d 1043, 1048 (5th Cir. 1981). To hold

that FDA may not regulate drugs made by physicians because doing so might affect the practice of medicine would, in effect, exempt physicians from the requirements of the FDCA. Nothing in the language or history of the FDCA countenances that result; to the contrary, the statute expressly contemplates that some physicians will manufacture drugs that are subject to regulation. *See* 21 U.S.C. § 360(b), (g)(2) (exempting from the requirement that drug manufacturers register with FDA licensed practitioners "who manufacture, prepare, propagate, compound, or process drugs or devices solely for use in the course of their professional practice"); *id.* § 374(a)(2)(B) (narrowing FDA's ability to review records when inspecting licensed practitioners "who manufacture, prepare, propagate, compound, or process drugs[] . . . solely for use in the course of their professional practice").

The district court similarly misapprehended 21 U.S.C. § 396, which is the only provision in the FDCA that contains the phrase the "practice of medicine" (and there only in the section's title). *See* 21 U.S.C. § 396 ("Practice of Medicine"). That provision is about medical devices, not drugs. *See id.* It concerns physician prescriptions of an FDA-approved or cleared device for uses not approved or cleared by the agency, *see id.* §§ 360(k), 360e—so-called "off label" prescriptions—and states that "[n]othing in this [Act] shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship." *Id.* § 396. With respect to drugs, FDA's longstanding position is that, with certain

limited exceptions, healthcare professionals may choose to prescribe or use a legally marketed human drug for an unapproved or "off label" use when they judge that the unapproved use is medically appropriate for an individual patient. But neither the statutory provision on which the district court relied, nor FDA's longstanding position entitles defendants to manufacture and use a drug that FDA has not approved for any use.

Contrary to the district court's suggestion (1-ER-18-19), it is irrelevant that each customized SVF treatment cannot be "mass produced" or that drugs comprising only human cells may not be patentable. Nothing in the definition of "drug" depends on either of these considerations. To the contrary, the Act applies even to drugs made on an individual basis, such as drugs that are "compounded" by a pharmacy or physician "for an identified individual patient." 21 U.S.C. § 353a. And the limits of patent eligibility have no evident bearing on the definition of a drug. The district court relied, in particular, on the proposition that a "product of nature" is "not patent eligible merely because it has been isolated," *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 580 (2013). But whether or not a drug is a product of nature or is patent eligible has little if anything to do with whether it fits the statutory definition of a drug or whether Congress would have wanted it to be marketed as a method for curing disease without any assessment of whether it is safe and effective for its intended use.

II. Defendants' SVF Product Is Not Entirely Excepted From FDA Regulation Under The Same Surgical Procedure Exception

The district court similarly erred when holding that defendants' treatments are entirely exempt from any FDA regulation so long as defendants create and then use the SVF within one visit to a clinic. Because the same surgical procedure exception is exactly that, "an exemption from the otherwise applicable provisions of the FDCA," defendants "ultimately bear the burden of establishing that it applies." *Regenerative Scis.*, 741 F.3d at 1322 (applying a different regulatory exception) (citing *United States v. First City Nat'l Bank of Houston*, 386 U.S. 361, 366 (1967) (stating the "general rule" of statutory construction that the party who "claims the benefits of an exception to the prohibition of a statute" carries the burden of establishing that the exception applies)). Defendants have not met and cannot meet that burden. As the Eleventh Circuit recently held, when doctors remove adipose tissue and then implant SVF, they are not subject to the same surgical procedure exception and are accordingly subject to some form of FDA regulation. *U.S. Stem Cell*, 998 F.3d at 1308-1310 (considering and rejecting the district court's summary-judgment ruling in this case).

A. The Text, Structure, History, and Purpose of the Exception Unambiguously Exclude Defendants' Activities

1. The same surgical procedure exception provides that any "establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure" is excepted from 21 C.F.R. Part 1271. 21 C.F.R. § 1271.15(b). FDA has defined HCT/P's as "articles containing or consisting

of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." *Id.* § 1271.3(d).

The text of these regulations makes clear that defendants' activity is outside the scope of this exception. The HCT/P that defendants remove from patients is adipose tissue, which is the relevant "article containing . . . human cells or tissues." The exception applies only if defendants subsequently implant "such HCT/P[]" into the patient. 21 C.F.R. § 1271.15(b). As the Eleventh Circuit explained in a similar case, the word "such" "is typically used to refer back to an antecedent," and "[h]ere, this means the HCT/Ps implanted must be the same as the antecedent HCT/Ps—that is, the HCT/Ps that were removed." *U.S. Stem Cell*, 998 F.3d at 1309; *see Such*, Black's Law Dictionary (11th ed. 2019) (defining "such" as "[t]hat or those; having just been mentioned"). But defendants do not implant adipose tissue into the patient. They implant a fundamentally different article, SVF. *U.S. Stem Cell*, 998 F.3d at 1310.

In particular, defendants use several enzymes to digest the adipose tissue, put the remaining product in a centrifuge and through a strainer multiple times, and add a saline solution to the digested, centrifuged, and strained product. *See, e.g.*, 6-ER-701-720; 6-ER-754-757; 10-ER-1604-1643. As a result, many components of the adipose tissue are discarded, and what remains is a different product consisting of various kinds of cells that were dispersed and embedded throughout adipose tissue, as well as cellular debris. *See, e.g.*, 6-ER-756-757; 7-ER-1054; 8-ER-1252-1253.

Thus, as the Eleventh Circuit explained, "[b]y the time the stromal-vascular fraction is reinjected, it is no longer 'such HCT/P' as the adipose tissue removed from the patient." *U.S. Stem Cell*, 998 F.3d at 1310; *see id.* at 1309 ("If significant processing steps expose the HCT/Ps to foreign substances and alter their form prior to reimplantation, then the HCT/Ps cease to be the same as they were at the time of removal.").

2. The context, structure, history, and purpose of FDA's regulations confirm this conclusion. *See Safari Club Int'l v. Haaland*, 31 F.4th 1157, 1171 (9th Cir. 2022) ("[O]ur task is to interpret the regulation as a whole, in light of the overall statutory and regulatory scheme[.]"). The same surgical procedure exception is part of a comprehensive regulatory scheme that aims to ensure proper regulation of products that could endanger the public health and safety and that does so through a "tiered, risk-based approach to regulating HCT/P's." 66 Fed. Reg. 5447, 5449 (Jan. 19, 2001). Ordinarily, HCT/P's are subject to a range of FDA regulations. *See* 21 C.F.R. § 1271.20; *see generally id.* pt. 1271, subparts C, D. FDA has established a lower tier of regulation that permits reduced FDA oversight of HCT/P's that are, among other things, "minimally manipulated." *Id.* § 1271.10(a)(1); *see id.* § 1271.10(b); *see generally id.* pt. 1271, subparts E, F. And FDA has also established complete exceptions to regulation, which include the same surgical procedure exception, where an establishment that uses HCT/P's is excepted from FDA's HCT/P regulations altogether. *See id.* § 1271.15.

Defendants' activities must be understood in the context of this tiered framework. As noted, HCT/P's may be subject to a lower tier of regulation if they are, among other things, "minimally manipulated." 21 C.F.R. § 1271.10(a)(1). For "structural tissue" like adipose tissue, minimal manipulation means "processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement." *Id.* § 1271.3(f)(1). Here, there can be no serious dispute that the adipose tissue is more than minimally manipulated when it is transformed into SVF, such that the resulting SVF would not be eligible for the lower tier of regulation under 21 C.F.R. § 1271.10. It would be strange to conclude that SVF, despite having been significantly manipulated—indeed, manipulated too much to qualify for the lower tier of regulation—is exempt altogether from regulation on the ground that it is, in fact, such HCT/P that was removed from the patient.

Reading the same surgical procedure exception to apply despite significant manipulation of the HCT/P that was removed would also create a stark contrast with the other complete exceptions from regulation, which do not apply where establishments significantly manipulate an HCT/P and then implant it into a patient. In addition to the same surgical procedure exception, on which defendants rely, 21 C.F.R. § 1271.15 creates complete exceptions for an establishment that "uses HCT/P's solely for nonclinical scientific or educational purposes," 21 C.F.R. § 1271.15(a), "accepts, receives, carries, or delivers HCT/P's in the usual course of business as a carrier," *id.* § 1271.15(c), only "receives or stores" HCT/P's for use within

the facility, *id.* § 1271.15(d), or "recovers" and "immediately transfers" "reproductive cells or tissue," "into a sexually intimate partner," *id.* § 1271.15(e). These other, narrow exceptions are in in the very same section of the regulations. They provide a further contextual indication that FDA did not create, through the same surgical procedure exception, a license to engage in nearly limitless manipulation and recombination of cells and tissues and implant the resulting articles into patients without any FDA oversight whatsoever.

The history and purpose of the same surgical procedure exception further underscore this conclusion. *See U.S. Stem Cell*, 998 F.3d at 1309-1310. FDA's 1997 proposed approach explained that the same surgical procedure exception aimed to capture only those activities where the "safety and effectiveness risks" would be no different than the risks "typically associated with surgery." 1997 Proposed Approach 12. Thus, in its proposed rule, FDA explained that the exception aimed to capture the sort of situation in which "a surgeon might remove a saphenous vein from a patient for use in a later coronary bypass in the same patient." 63 Fed. Reg. 26,744, 26,748 (May 14, 1998). The purpose of the exception was not to allow establishments to create new substances through extensive chemical and physical modification to HCT/P's and then implant them into patients, free of all regulatory obligations under the FDCA and the PHSA. New products created based on such extensive manipulations pose risks to patient health and safety that are qualitatively different from, and greater than, those typically associated with surgery. Indeed, although FDA

is not required to show evidence of patient harm to prevail in this case, the record includes examples of patients suffering serious complications after undergoing defendants' treatments. *See* 10-ER-1499-1500; *see, e.g.*, 8-ER-1099-1102; 10-ER-1515-1519; 10-ER-1561-1562; *see also* 7-ER-860-861 (noting the absence of proper procedures to identify, record, and track adverse events).

In 1997, when FDA first proposed its current regulatory approach to HCT/P's, FDA explained that "[c]ells and tissues that were manipulated extensively" or "combined with non-tissue components" would be "regulated as biologics or devices requiring premarket approval by FDA." 1997 Proposed Approach 7. In 2001, following notice-and-comment rulemaking, FDA issued its final rule on HCT/P's. 66 Fed. Reg. 5447. The preamble to that rule clarified that "hospitals that store autologous cells or tissues for subsequent application in the same patient" would qualify for the same surgical procedure exception "so long as the hospital does not engage in any other activity encompassed within the definition of 'manufacture.'" *Id.* at 5460; *see* 21 C.F.R. § 1271.3(e) (defining "manufacture"). There can be little doubt that defendants' manufacturing process, which involves extensive manipulation and processing of adipose tissue and addition of non-tissue components, was not what FDA contemplated when it promulgated the same surgical procedure exception.

3. Defendants acknowledge that they remove adipose tissue and implant SVF. Defendants do not urge that they implant adipose tissue, as opposed to SVF, into patients or that adipose tissue and SVF are one and the same. Rather, they argue that

they remove HCT/P's from patients and implant "such HCT/P's" because in the process of removing adipose tissue, they remove each of the individual cells that exist in adipose tissue and later end up in the final SVF product. Thus, in defendants' view, so long as they create and implant a product that comprises cells or other component parts taken from a patient, and they do so in one extended procedure, FDA has entirely excepted them from regulation, regardless of whether the resulting article bears any resemblance to the tissue that was removed.

Defendants' interpretation of the same surgical procedure exception rests on an implausible reading of the regulation. As a matter of plain text, that exception applies to an establishment that "removes HCT/P's" from an individual and implants "such HCT/Ps" into the same individual. 21 C.F.R. § 1271.15(b). The "remove[d] HCT/P[]" must therefore be the "HCT/P[]" that is later implanted. *Id.* But defendants remove one HCT/P—adipose tissue—and implant another HCT/P—an SVF product comprising various cells that were once dispersed and embedded in adipose tissue. Defendants cannot evade the terms of this narrow exception by noting that all tissues are collections of cells and that when they implant an HCT/P that includes cells (among other things), those cells were at some point in the patient. That disregards the regulation's focus on the HCT/P that an establishment "removes." *Id.* Defendants' argument requires believing that the "remove[d] HCT/P[]" does not refer to the HCT/P that was actually removed but instead to whatever portion or components of that HCT/P defendants then isolate through extensive processing and choose to

implant. It would be odd to suggest that the composition of the HCT/P that was removed—here, adipose tissue—has no bearing on whether the establishment has implanted "such HCT/Ps" into the patient. *Id.*

Defendants' interpretation of the same surgical procedure exception is also highly implausible as a matter of context and history. As discussed, FDA's regulatory scheme creates a tiered, risk-based approach that repeatedly focuses on whether and how much HCT/P's are manipulated. Defendants, however, would read the same surgical procedure exception—a complete exemption from FDA regulation—as permitting any establishment to remove any tissue from any part of a patient, perform any number and type of manufacturing steps on that tissue (regardless of the risk associated with any of those steps), and then invoke the same surgical procedure exception to free itself from all FDA oversight as long as the end product contained cells that were present in the original tissue. That expansive interpretation of the exception would drastically limit FDA oversight and cannot be squared with the regulatory scheme as a whole.

Defendants' interpretation is particularly implausible because they are removing a structural tissue (adipose) and implanting a collection of cells. Not only does the same surgical procedure exception require implanting "such HCT/Ps" into the same individual, 21 C.F.R. § 1271.15(b), but the regulatory scheme repeatedly distinguishes between "tissues" and "cells." *See* 21 C.F.R. § 1271.3. Thus, the regulations define HCT/P's to mean "articles containing or consisting of human *cells* or *tissues* that are

intended for implantation, transplantation, infusion, or transfer into a human recipient." *Id.* § 1271.3(d)(3) (emphasis added). And, as referenced above, to determine whether an HCT/P is "minimally manipulated," one of the criteria for limited FDA regulation under 21 C.F.R. § 1271.10(a)(1), FDA's regulations distinguish between types of HCT/P's—"structural tissue" and "cells or nonstructural tissues." *Id.* § 1271.3(f). The regulations set out different definitions for the "[m]inimal manipulation" of structural tissue and the "[m]inimal manipulation" of cells and other tissues. *Id.* Defendants' reading of the same surgical procedure exception as allowing them to transform structural tissues into new products comprising cells would undermine that distinction.

4. The district court adopted defendants' interpretation of the same surgical procedure exception not by parsing the exception itself, 21 C.F.R. § 1271.15(b), but instead by looking to the general definition of an HCT/P in 21 C.F.R. § 1271.3(d), which is applicable throughout the provisions governing regulation of HCT/P's. As noted, the regulations define HCT/P's to mean "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." 21 C.F.R. § 1271.3(d).

The district court drew the wrong inference from the definitional reference to both tissues and cells. The district court stated that cells cannot be removed separate from surrounding tissue or larger systems and concluded that FDA's approach of looking to "the largest system that was removed" would therefore render references to cells "superfluous." 1-ER-32; *see* 1-ER-16. Each step of that analysis was mistaken.

The record gives an example of removing cells in isolation: a "human ovocyte." 6-ER-767. The regulations could also reasonably allow for the possibility that over time scientists will develop a greater ability to extract cells in isolation. More to the point, even if cells could never be removed in isolation, the district court's conclusion would not follow. The definition of HCT/P's applies throughout the entire regulatory structure governing HCT/P's. *See* 21 C.F.R. § 1271.3 (establishing definitions for 21 C.F.R. Part 1271). This includes a litany of other regulatory provisions that govern the listing, manufacture, and storage of human cells, tissues, and cellular and tissue-based products. Thus, even if the word "cells" in the definition of HCT/P's in § 1271.3(d) served no function in the same surgical procedure exception, the inclusion of that term in this broadly applicable definition would not be surplusage, as the district court mistakenly concluded.

To the extent that the definition of HCT/P's sheds any light on the meaning of the same surgical procedure exception, it cuts against defendants' interpretation. By defining HCT/P's as "articles containing or consisting of cells or tissues," the definition acknowledges that an HCT/P will often be a larger article that is made up of component cells—here, adipose tissue. And, as discussed, the fact that the definition expressly distinguishes between cells and tissues also further calls into question defendants' effort to remove a tissue (here, adipose) but then extensively process that tissue to create a collection of certain cells and conceptualize the HCT/P or HCT/P's they removed as a collection of cellular parts. Human tissues are composed of cells, so if the relevant

unit of analysis were the cell, the reference to tissues would be unnecessary. The same surgical procedure exception is thus best read to require that if tissues are removed, "such [tissues]" must be implanted. 21 C.F.R. § 1271.15(b). If anything, it is the district court's reading that renders the use of the word "tissues"—and, for that matter, the phrase "articles containing or consisting of human cells or tissues," *id.* § 1271.3(d)—superfluous, by treating the cells rather than the tissues or articles in which they appear as the relevant HCT/P's.

The district court also stated that "[m]ost critically, the definition of HCT/Ps states that HCT/Ps are 'articles . . . **intended for** implantation, transplantation, infusion, or transfer into a human recipient.'" 1-ER-14 (second alteration in original) (court's emphasis) (quoting 21 C.F.R. § 1271.3(d)). The court, however, did not explain why the term "intended for" in the definitional provision supports the court's parsing of the same surgical procedure exception or is "[m]ost critical[]" to the court's conclusion. The district court did not adopt defendants' argument that because they do not intend to implant adipose tissue, adipose tissue is not an HCT/P at all and the only HCT/P's being removed are whatever cells defendants intend to implant that are, at the time of removal, dispersed and embedded throughout the adipose tissue. The court made clear that "[t]he adipose tissue Defendants remove from patients to produce their [California Stem Cell Treatment Center] products is an HCT/P." 1-ER-15. The fact that defendants had no intention of implanting the adipose tissue that they removed counsels against, rather than in favor of, the applicability of the same surgical procedure

exception. And it would turn the exception on its head to suggest that defendants may contravene the natural reading and clear purpose by declaring that their intent should be evaluated for each cell individually.

B. FDA's Interpretation of its Regulation is, at a Minimum, Entitled to Deference

As discussed, FDA's interpretation is the most natural reading of the text and the only one that makes sense in context, and it should be upheld on that ground. *See U.S. Stem Cell*, 998 F.3d at 1310 ("we hold the same surgical procedure exception unambiguously does not apply"); *cf. Mountain Cmtys. for Fire Safety v. Elliott*, 25 F.4th 667, 676-677, 676 n.3 (9th Cir. 2022) (declining to consider deference where the "'traditional tools' of construction" provide a clear answer) (quoting *Kisor v. Wilkie*, 139 S. Ct. 2400, 2415 (2019)). But even if the regulation were considered to be ambiguous, FDA's interpretation would be entitled to deference under *Kisor v. Wilkie*, 139 S. Ct. 2400, and *Auer v. Robbins*, 519 U.S. 452 (1997). In *Kisor*, the Supreme Court clarified that what had previously been known as "*Auer* deference" is appropriate in defined circumstances. Were the governing regulation ambiguous here, the Supreme Court's explanation of when such deference is appropriate neatly fits the circumstances of this case, and it would be appropriate to defer to FDA's official, considered, and expert view.

1. As the Supreme Court recently reaffirmed, deference is owed "to agencies' reasonable readings of genuinely ambiguous regulations" in certain circumstances.

Kisor, 139 S. Ct. at 2408; *see Auer*, 519 U.S. at 461; *Bowles v. Seminole Rock & Sand Co.*, 325 U.S. 410, 413-414 (1945). That form of interpretive deference, often referred to as *Auer* deference, is particularly warranted where the agency's interpretation "necessarily require[s] significant expertise and entail[s] the exercise of judgment grounded in policy concerns." *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994); *see Love v. Marriott Hotel Servs., Inc.*, 40 F.4th 1043, 1047 (9th Cir. 2022).

In *Kisor*, the Supreme Court declined to overturn *Auer* deference. *Kisor*, 139 S. Ct. at 2408. The Court concluded that "*Auer* deference retains an important role in construing agency regulations." *Id.* In upholding *Auer*, the Court "reinforce[d] its limits," emphasizing various criteria that an agency must meet in order to receive such deference. *Id.* Chief among those criteria is that deference is not appropriate unless the regulation is "genuinely ambiguous" after taking into account "all the 'traditional tools' of construction." *Id.* at 2415. *Auer* deference comes into play only "[i]f genuine ambiguity remains," and only if, after examining the "text, structure, [and] history" of the regulation, the agency's interpretation is "reasonable." *Id.* at 2415-2416. In deciding whether to accord deference, a court must determine whether the regulatory position reflects the agency's "authoritative" or "official position," rather than "any more ad hoc statement not reflecting the agency's views." *Id.* at 2416. It must decide whether the agency's interpretation "implicate[s] its substantive expertise." *Id.* at 2417. And it must ensure that the interpretation reflects the agency's "fair and considered judgment" and is not merely a "*post hoc* rationalizatio[n] advanced" to "defend past agency action against

attack." *Id.* (alteration in original) (quoting *Christopher v. SmithKline Beecham Corp.*, 567 U.S. 142, 155 (2012)).

2. Here, even if FDA's interpretation of its regulation were thought to be ambiguous, it should be upheld as reasonable and entitled to deference. For the reasons stated above, FDA's reading of its own regulation is, at a minimum, a reasonable interpretation given the text, structure, history, and purpose of the regulations. And FDA's interpretation satisfies all of the criteria that courts must assess in determining whether the "character and context of the agency interpretation entitles it to controlling weight." *See Kisor*, 139 S. Ct. at 2416.

FDA's interpretation of the same surgical procedure exception represents the agency's "official position." *Kisor*, 139 S. Ct. at 2416. FDA has consistently explained that the same surgical procedure exception is a narrow one and that an establishment qualifies for the exception when it implants into an individual the HCT/P in its original form, subject only to very minimal processing steps, such as rinsing, cleansing, sizing, or shaping. FDA Guidance 5. The guidance document announcing the agency's position explains that it "represents the current thinking of [FDA] on this topic," and that it provides the agency's "current interpretation of this regulation and includes examples based on inquiries received by the Agency" since 2001. *Id.* at 1. The 2017 guidance document finalizes the draft guidance first issued in 2014. *Id.* And it is made available on a website that "lists all official FDA Guidance Documents and other regulatory guidance." *See* FDA, *Search for FDA Guidance Documents*,

https://perma.cc/9VCK-8YBK. It is therefore beyond dispute that the document is not an "ad hoc statement not reflecting the agency's views." *Kisor*, 139 S. Ct. at 2416.

FDA's interpretation also plainly "implicate[s] its substantive expertise." *Kisor*, 139 S. Ct. at 2417. The *Kisor* Court noted that "technical" regulations are especially deserving of deference and gave as an example FDA's interpretation of regulations concerning which substances qualified as a "moiety." *Id.*; *see id.* at 2410-2411 (plurality op.). FDA's interpretation of regulations concerning HCT/P's is equally technical and equally implicates the agency's substantive expertise regarding the safety and effectiveness of substances administered to patients for therapeutic purposes. After all, the purpose of the exception, when it applies, is to except establishments whose use of cell or tissue products poses no greater risk than ordinary surgery. Determining the risks associated with particular types of HCT/P's, and the circumstances surrounding their handling and processing, is squarely within the competence of an agency charged to "protect the public health." 21 U.S.C. § 393(b)(2).

FDA's interpretation also reflects the agency's "fair and considered judgment." *Kisor*, 139 S. Ct. at 2417. The interpretation at issue here is not a post hoc rationalization first announced in litigation. Rather, the guidance document at issue here was published well before the filing of this complaint. It previously spent three years in draft form; in accordance with FDA's guidance practices, FDA published the draft guidance in the Federal Register and allowed oral and written comments on the guidance. 81 Fed. Reg. 23,661 (Apr. 22, 2016); 79 Fed. Reg. 63,348 (Oct. 23, 2014); *see* 21 C.F.R. § 10.115

(explaining FDA's guidance practices). And the guidance document is entirely consistent with all of FDA's statements on this topic, starting with the proposed approach it issued in 1997. *See supra* pp. 6-8, 30-31. Additionally, given that defendants were well aware of a warning letter sent to one of their affiliates several years before FDA filed this action, *see, e.g.*, 2-ER-62, there is no risk that FDA's interpretation creates "unfair surprise" to defendants. *Kisor*, 139 S. Ct. at 2418.

For all of these reasons, this is a case where *Auer* deference "enables the agency to fill out the regulatory scheme Congress has placed under its supervision." *Kisor*, 139 S. Ct. at 2418. *Auer* deference gives FDA "significant leeway to say what its own rules mean." *Id.* Here, that means that FDA's reasonable interpretation of the same surgical procedure exception would control even if that interpretation were not unambiguously correct.[4]

[4] If *Auer* deference did not apply, FDA's interpretation would be entitled to deference under *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944), to the extent that it had the "power to persuade." *Id.* at 140. FDA's interpretation is persuasive for the reasons explained above.

CONCLUSION

For the foregoing reasons, the judgment of the district court should be vacated and the case should be remanded.

Respectfully submitted,

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MAY 2023

STATEMENT OF RELATED CASES

Pursuant to Ninth Circuit Rule 28-2.6, appellant is unaware of any related case pending in this Court.

s/ Adam Jed
ADAM C. JED

CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limit of Federal Rule of Appellate Procedure 32(a)(7)(B) because it contains 10,363 words. This brief also complies with the typeface and type-style requirements of Federal Rule of Appellate Procedure 32(a)(5)-(6) because it was prepared using Word for Microsoft 365 in Garamond 14-point font, a proportionally spaced typeface.

s/ Adam Jed
ADAM C. JED

ADDENDUM

TABLE OF CONTENTS

21 U.S.C. § 321 (excerpt)

§ 321. Definitions; generally

For the purposes of this chapter—

* * *

(g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia,1 official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 343(r)(1)(B) and 343(r)(3) of this title or sections 343(r)(1)(B) and 343(r)(5)(D) of this title, is made in accordance with the requirements of section 343(r) of this title is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 343(r)(6) of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement.

* * *

21 C.F.R. § 1271.3 (excerpts)

§ 1271.3 How does FDA define important terms in this part?

The following definitions apply only to this part:

* * *

(d) *Human cells, tissues, or cellular or tissue-based products (HCT/Ps)* means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and

semen or other reproductive tissue. The following articles are not considered HCT/Ps:

(1) Vascularized human organs for transplantation;

(2) Whole blood or blood components or blood derivative products subject to listing under parts 607 and 207 of this chapter, respectively;

(3) Secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered an HCT/P;

(4) Minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow);

(5) Ancillary products used in the manufacture of HCT/P;

(6) Cells, tissues, and organs derived from animals other than humans; and

(7) In vitro diagnostic products as defined in §809.3(a) of this chapter.

(8) Blood vessels recovered with an organ, as defined in 42 CFR 121.2, that are intended for use in organ transplantation and labeled "For use in organ transplantation only."

* * *

(f) *Minimal manipulation* means:

(1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and

(2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

* * *

21 C.F.R. § 1271.10

§ 1271.10 Are my HCT/P's regulated solely under section 361 of the PHS Act and the regulations in this part, and if so what must I do?

(a) An HCT/P is regulated solely under section 361 of the PHS Act and the regulations in this part if it meets all of the following criteria:

(1) The HCT/P is minimally manipulated;

(2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

(3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

(4) Either:

(i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

(ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

(*a*) Is for autologous use;

(*b*) Is for allogeneic use in a first-degree or second-degree blood relative; or

(*c*) Is for reproductive use.

(b) If you are a domestic or foreign establishment that manufactures an HCT/P described in paragraph (a) of this section:

(1) You must register with FDA;

(2) You must submit to FDA a list of each HCT/P manufactured; and

(3) You must comply with the other requirements contained in this part.

21 C.F.R. § 1271.15

§ 1271.15 Are there any exceptions from the requirements of this part?

(a) You are not required to comply with the requirements of this part if you are an establishment that uses HCT/P's solely for nonclinical scientific or educational purposes.

(b) You are not required to comply with the requirements of this part if you are an establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure.

(c) You are not required to comply with the requirements of this part if you are a carrier who accepts, receives, carries, or delivers HCT/P's in the usual course of business as a carrier.

(d) You are not required to comply with the requirements of this part if you are an establishment that does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/P's solely for implantation, transplantation, infusion, or transfer within your facility.

(e) You are not required to comply with the requirements of this part if you are an establishment that only recovers reproductive cells or tissue and immediately transfers them into a sexually intimate partner of the cell or tissue donor.

(f) You are not required to register or list your HCT/P's independently, but you must comply with all other applicable requirements in this part, if you are an individual under contract, agreement, or other arrangement with a registered establishment and engaged solely in recovering cells or tissues and sending the recovered cells or tissues to the registered establishment.